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Body mass index and risk of renal cell cancer: A dose-response meta-analysis of published cohort studies

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Obesity is accepted as one of the major risk factors for renal cell cancer (RCC). However, conflicting results persist for the pooled risks based on the results from case–control and cohort studies combined, and the exact shape of the dose–response relationship has not been clearly defined yet. To help elucidate the role of obesity, PubMed and Embase databases were searched for published cohort studies on associations between body mass index (BMI) and risk of RCC. Random-effects models and dose-response meta-analyses were used to pool study results. Subgroup analyses were conducted by the available characteristics of studies and participants. Cohort studies (21) with 15,144 cases and 9,080,052 participants were identified. Compared to normal weight, the pooled relative risks and the corresponding 95% confidence intervals of RCC were 1.28(1.24–1.33) for preobesity and 1.77(1.68–1.87) for obesity, respectively. A nonlinear dose–response relationship was also found for RCC risk with BMI ($p = 0.000$), and the risk increased by 4% for each 1 kg/m^2 increment in BMI. There was no significant between-study heterogeneity among studies ($I^2 = 35.6\%$ for preobesity and $I^2 = 44.2\%$ for obesity, respectively). Subgroup analysis showed a basically consistent result with the overall analysis. These results suggest that increased BMI are associated with increased risk of RCC both for men and women.

Renal cell cancer (RCC), which accounts for 2–3% of all adult malignant neoplasms, is the most lethal of the common urologic cancers.[1] Traditionally, 30–40% of patients with RCC have died of their cancer.[1] The incidence of RCC has been increasing both in the US and in most Western countries.[2–4] The incidence varies more than 10-fold over the world. The highest rates are found in North America and Europe and the lowest in Asia.[5] RCC occurs about twice as often among men, as among women.

It is reported that the rising incidence of RCC is due both to an increased prevalence of risk factors and to improvements in diagnosis.[6] Obesity is now accepted as one of the major risk factors for RCC.[1] Although an association between body mass index (BMI) and increased RCC risk is consistently observed, conflicting results persist for the pooled risks based on the results from case–control and cohort studies combined.[7–9] Bergström *et al.*[7] reported that increased BMI is equally strongly associated with an increased risk of RCC among men and women, whereas Mathew *et al.*[9] showed a slightly higher risk of renal cancer in women than in men. In addition, the exact shape of the dose–response relationship between BMI and RCC risk has not been clearly defined.

In our study, we carried out a dose-response meta-analysis on BMI and risk of RCC by summarizing the results of published cohort studies. Our aim was to update and quantitatively assess the association between them, and to examine the possibility of the nonlinear associations.

Material and Methods

Search strategy

We searched PubMed and Embase databases to December 15, 2013 for studies on the relationship between BMI and incidence of RCC. The same search strategy was applied to Embase as that used for PubMed (see Appendix A) using the appropriate controlled vocabulary. Our search was limited to cohort studies in humans. No lower date or "language" limits were set. We also reviewed the reference lists from reviews, meta-analyses, and other relevant publications to search for additional relevant studies.

Eligibility criteria

Studies were included in this dose-response meta-analysis if they met the following criteria: (*i*) use of cohort design, (*ii*) BMI, obesity, or weight as the exposure of interest, (*iii*) RCC as the outcome of interest, and (*iv*) reporting risk estimates with the corresponding 95% confidence intervals (95%CIs) or sufficient information to calculate them. For dose–response analysis, the study had to report the estimates for at least three BMI categories. Studies on particular subtype of RCC (*i.e.,* clear cell RCC) were excluded. If data were duplicated

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What's new?

Obesity is known to be a major risk factor for renal-cell cancer (RCC). However, various studies have yielded conflicting results regarding the exact impact of increasing body mass index (BMI) on RCC risk. In this study, the authors conducted a dose-response meta-analysis of all published cohort studies involving BMI and risk of RCC. They found that, compared to normal weight, obesity conferred a relative risk of 1.77 for RCC, and that risk increased by 4% for each 1kg/m2 increment in BMI.

in more than one study, only the most recent and informative one was included.

Data extraction

The following data were extracted from each study: first author's surname, publication year, study location, study name or source, study period, duration of follow-up, sex, age, study size (number of cases, participants or person-years), assessment method of weight/height (measured or self-reported), BMI categories, risk estimates with the corresponding 95%CIs for each BMI category, and adjustment factors in the multivariable analysis. We assumed that rate ratio and hazard ratio were all valid estimates of the relative risks (RRs), and we, therefore, reported all results as RR for simplicity. We extracted the RRs from the maximally adjusted model to reduce the risk of possible residual confounding.

The median or mean level of BMI for each category was assigned to the corresponding RR. When the median or mean BMI per category was not reported in the study, we assigned the midpoint of the upper and lower boundaries in each category as the average level. If the upper boundary for the highest category or the lower boundary for the lowest category was not provided, we assumed that the boundary had the same amplitude as the adjacent category. The BMI (kg/m^2) in adults was classified as follows[10]: normal weight, 18.50–24.99; preobesity, 25.00–29.99; obesity, $\geq$30.00.

When a study reported risk estimates and 95%CIs relative to a reference category other than the lowest normal weight, the RRs were recalculated using the lowest one as reference by the method proposed by Greenland and Longnecker.[11] Briefly, consider a cohort study with B_0 unexposed subjects and B_i subjects exposed at level i ($i = 1, \ldots, n$), of whom A_0 and A_i subjects, respectively, developed the disease being studied. The log RRs were approximately equal to $\log_e(R_i) = \log_e(A_iB_0/A_0B_i)$. The variance was estimated as $V_i = 1/A_0 + 1/B_0 + 1/A_i + 1/B_i$ and approximate 95%CIs for the log RRs were $\log_e(R_i) \pm 1.96V_i$.

Statistical analysis

We conducted separate meta-analysis for different levels of BMI. For the outcome of interest, pooled estimates and 95%CIs of effect sizes were calculated by using an inverse-variance weighted random-effects meta-analysis.[12] The I^2 statistic was used to assess heterogeneity among studies,[13] and I^2 values of 0, 25, 50 and 75% represent no, low, moderate and high heterogeneity, respectively. To investigate the effect of potential confounders, subgroup analyses were conducted by the available characteristics of studies and participants, if three or more studies were available per subgroup.

For dose-response analysis, a two-stage random-effects dose-response meta-analysis[14] was performed to compute the trend from the correlated log RR estimates across levels of BMI, taking into account the between-study heterogeneity. In the first stage, a restricted cubic spline model with three knots at percentiles 10, 50 and 90% of the distribution was estimated using generalized least-square regression taking into account the correlation within each set of published RRs. Then, the study-specific estimates were combined using the restricted maximum likelihood method in a multivariate random-effects meta-analysis.[15] A p value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero.[16]

Considering the possibility of effect modification by other known risk factors (*i.e.*, sex, age, smoking, and hypertension), we also conducted dose-response meta-analyses by these factors, respectively, apart from subgroup analyses. Furthermore, we performed two sensitivity analyses to assess whether the summary estimates are robust to inclusion of studies: first, one study at a time was removed and the rest analyzed to evaluate whether the results could have been affected significantly by a single study[17]; second, other percentiles (5, 35, 65 and 95%) of the distribution were used as knots for dose–response meta-analysis. Publication bias was evaluated with the use of the Begg and Egger's test.[18,19] In case of evidence of publication bias, we carried out a "trim and fill" analysis to evaluate if this could have affected the results.[20]

All statistical analyses were performed with Stata version 12 (Stata Corporation, College Station, TX). All reported probabilities (p values) were two-sided, with $p < 0.05$ considered statistically significant.

Results

Literature search and study characteristics

Our literature search identified 21 cohort studies[21–41] of BMI and RCC risk (Fig. 1). Combined, these studies included 15,144 cases and 9,080,052 participants. Nine studies[22,23,25,28,30,32,37,39,41] were conducted in the United States, eight[21,26,31,33–35,38,40] in Europe, and four[24,27,29,36] in Asia. Most studies controlled for age (17 studies[21–23,25,27–38,41]) and smoking (17 studies[21–23,25,27–38,41]). A few studies adjusted for

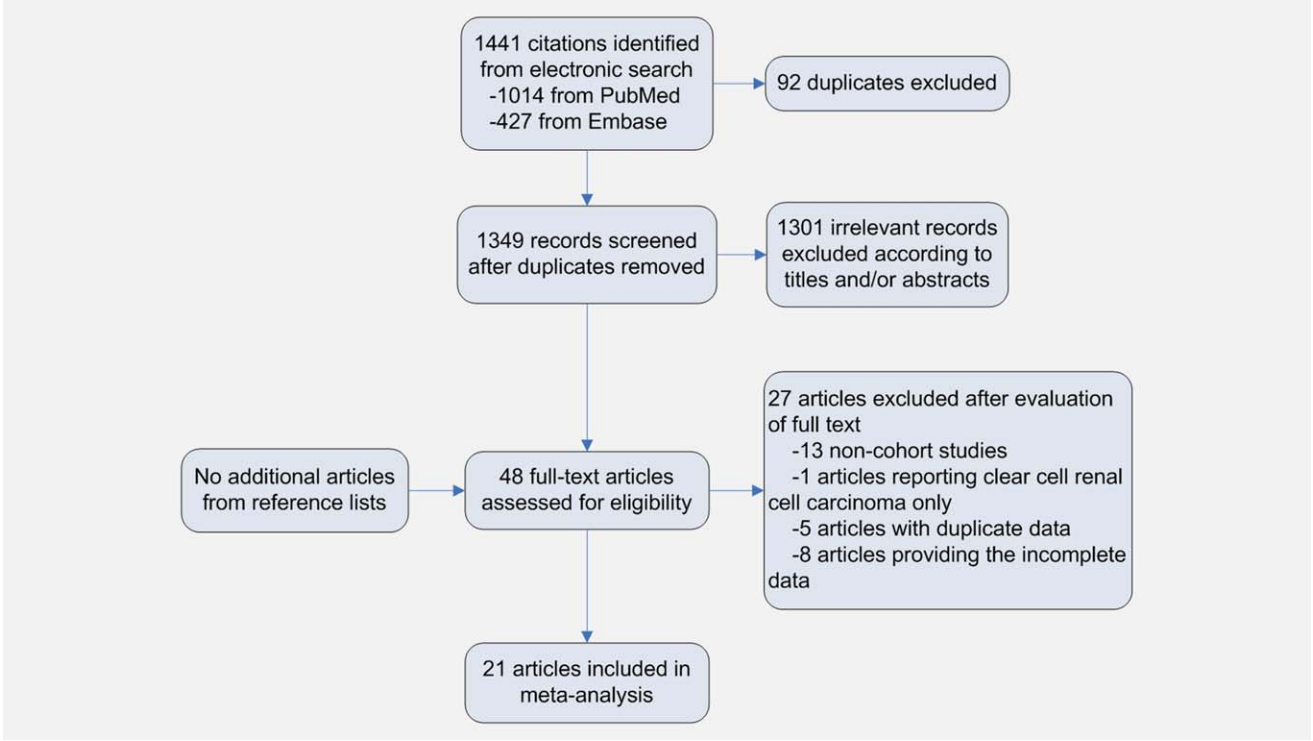

Figure 1. Flowchart of selection of studies for inclusion in this meta-analysis. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

physical activity (nine studies[27–31,34,36,38,41]), alcohol consumption (eight studies[25,27,29–31,34,36,41]), hypertension (seven studies[23,25,27,30,32,35,37]), and other factors. Three[24,35,36] and six[22,23,29,31,32,39] studies only reported separate outcomes of males and females, respectively, and 12 studies[21,25–30,33,34,37,38,40,41] reported outcomes of both sex. Of the 12 studies, nine[21,27,28,30,33,34,37,40,41] reported outcomes of males and females separately while three[25,26,38] provided data of males and females combined. Furthermore, women in one study[28] had been included in another one[23] and the latter was the most recent, so we excluded women of the former from meta-analysis. General characteristics in the studies included in this meta-analysis were shown in Table 1.

Quantitative synthesis

Abnormal vs. normal BMI. Compared to the reference category (normal weight), the combined RRs(95%CIs) of RCC were 1.28(1.24–1.33) and 1.77(1.68–1.87) for the category of preobesity and obesity, respectively (Fig. 2). No evidence of high heterogeneity among studies was found in the analyses (preobesity: $I^2 = 35.6\%$; obesity: $I^2 = 44.2\%$).

Subgroup analysis. For the category of preobesity and obesity, subgroup analysis showed a basically consistent result with the overall analysis (Table 2). The risk of RCC with preobesity and obesity was slightly high in women, in studies which located in Asia, in studies in which weight and height was self-reported, in studies not adjusting for age and in studies which adjusted for smoking and hypertension. No significant effect differences were observed for duration of follow-up and for other adjustment factors (*i.e.,* physical activity and alcohol consumption). For preobesity, some evidence of heterogeneity was found in men ($I^2 = 53.2\%$), in studies in which weight and height was measured ($I^2 = 50.2\%$), and in studies not adjusting for smoking ($I^2 = 65.4\%$). While for obesity, some evidence of heterogeneity was found in studies which located in North America ($I^2 = 54.1\%$), in studies in which weight and height was self-reported ($I^2 = 53.4\%$), in studies of which duration of follow-up was more than 10 years ($I^2 = 59.6\%$), and in studies not adjusting for age ($I^2 = 51.6\%$), smoking ($I^2 = 63.9\%$) and physical activity ($I^2 = 50.2\%$).

Dose–response meta-analysis. Dose-response from 21 cohort studies showed an increased RCC risk of 1.04(1.04–1.05) for each 1 kg/m^2 increase in BMI. When adjusted for sex, the risk of RCC for men and women increased by 4% (RR = 1.04, 95%CI = 1.03–1.05) and 5% (RR = 1.05, 95%CI = 1.04–1.06), respectively, for each 1 kg/m^2 increment.

As shown in Figure 3, some evidence of a nonlinear relationship between BMI and risk of RCC was found ($p = 0.000$). Compared to BMI = 18.5 kg/m^2, the summary RRs(95%CIs) of RCC were 1.16(1.12–1.20), 1.48(1.42–1.54), 2.03(1.89–2.16), and 2.77(2.48–3.10) for BMI = 25, 30, 35 and 40 kg/m^2, respectively. A statistically nonlinear relationship between BMI and RCC risk was also observed by adjustment of sex, age, smoking, and hypertension, as shown in Figure 4.

Sensitivity analysis. In a sensitivity analysis in which one study at a time was removed and the rest analyzed, the

Table 1. Study characteristics of published cohort studies on BMI and risk of RCC

Author, year, country	Study name or source, study period, duration of follow-up	Study size, sex, age, number of cases	Assessment method of weight/height	BMI (kg/m^2)	RR(95%CI)	Adjustment factors
Haggstrom *et al.*, 2013, Norway, Sweden and Austria,	Me-Can, NA, 10y	560,388(M 278,920; W 281,468), M/W, 42y, 855(M 592; W 263)	Self-reported	M 21.5 ± 1.3	M 1.00(Reference)	Categories of birth year, age at measurement, and stratified for cohort, smoking and quintiles of BMI (except for BMI and the composite score)
				23.8 ± 0.8	1.11(0.81–1.52)	
				25.4 ± 0.8	0.94(0.68–1.29)	
				27.1 ± 0.9	1.28(0.95–1.73)	
				31.7 ± 3.6	1.51(1.13–2.03)	
				W 20.0 ± 1.2	W 1.00(Reference)	
				22.2 ± 0.8	0.95(0.52–1.74)	
				24.1 ± 0.8	1.84(1.08–3.13)	
				26.4 ± 1.0	1.74(1.02–2.94)	
				31.7 ± 3.6	2.21(1.32–3.70)	
Kabat *et al.*, 2013, Canada	CNBSS, 1980–2000, NA	89,835, W, 49.0(40–59)y, 196	Measured	<21.6	1.00(Reference)	Age, oral contraceptive use, hormone therapy, menopausal, years of education, and pack-years of smoking
				21.6–23.2	0.93(0.56–1.56)	
				23.3–24.9	0.92(0.55–1.53)	
				25.0–27.8	1.54(0.97–2.43)	
				≥27.9	1.43(0.89–2.28)	
Karami *et al.*, 2013, USA	NIH-AARP, 1995–2006, 11.2y	NIH–AARP: 210,300, W, 62.3(50–71)y, 601	Self-reported	<25	NIH–AARP	BMI, highest educational level completed, race/ethnicity, history of hypertension, and smoking status
				25–30	1.00(Reference)	
				>30	1.41(1.15–1.74)	
					2.41(1.98–2.94)	
	PLCO, 1993–2001, 14.2y	PLCO: 73,652, W, 61.3(55–74)y, 191			PLCO 1.00(Reference)	
					1.54(1.07–2.24)	
					2.49(1.74–3.57)	
Leiba *et al.*, 2013, Israel	INCR, 1967–2005, 15.9(8.3–26.1) y	1,110,835, M, 16–19 y, 274	Measured	<22.5	1.00(Reference)	Birth year
				22.5–24.9	1.37(1.03–1.84)	

Table 1. Study characteristics of published cohort studies on BMI and risk of RCC (Continued)

Author, year, country	Study name or source, study period, duration of follow-up	Study size, sex, age, number of cases	Assessment method of weight/height	BMI (kg/m^2)	RR(95%CI)	Adjustment factors
				25.0–27.4	1.26(0.78–2.02)	
				≥27.5	2.63(1.67–4.1)	
Macleod *et al.*, 2013, USA	VITAL, 2000.10–2009.12.31, 8(0–9)y	73,440(M 37,095; W 40,165), M/W, 50–76y, 238(M 160; W 89)	Self-reported	<25	1.00(Reference)	Age, gender, ethnic group, hypertension, diabetes, kidney disease, viral hepatitis, smoking, alcohol consumption, fruit and vegetable intake
				25–29	1.23(0.88–1.72)	
				30–34	1.20(0.81–1.78)	
				≥35	1.71(1.06–2.79)	
Van Hemelrijck *et al.*, 2012, Sweden	AMORIS, 1985–1996, 13y	85,025, M/W, (M 55.46 ± 10.98y; W 43.93 ± 13.95y), 167	Measured	18.5–24.99	1.00(Reference)	NA
				25–29.99	1.37(1.00–1.89)	
				>30	1.06(0.58–1.93)	
Sawada *et al.*, 2010, Japan	JPHCPS, 1990–2006.12.31, 13.5y	99,462(M 46,837; W 52625), M/W, 40–69y, 139(M 101; W 38)	Self-reported	M < 21	M 1.86(1.01–3.45)	Age, public health center area, smoking status, alcohol drinking, leisure-time physical activity, history of hypertension and history of diabetes mellitus
				21–22.9	1.16(0.62–2.16)	
				23–24.9	1.00(Reference)	
				25–26.7	1.39(0.73–2.63)	
				≥27	1.99(1.04–3.81)	
				W < 21	W 1.04(0.43–2.56)	
				21–24.9	1.00(Reference)	
				>25	1.55(0.76–3.18)	
Adams *et al.*, 2008, USA	NIH-AARP, 1995–2003.12, >8.2y	528,772(M 313,522; W 215,250), M/W, 50–71y, 1366(M 1022; W 344)	Self-reported	18.5–22.5	M 1.00(Reference)	Age, smoking status and dose, physical activity, protein intake, and history of diabetes
				22.5–25	1.15(0.85–1.57)	
				25–27.5	1.43(1.07–1.92)	
				27.5–30	1.64(1.22–2.22)	
				30–35	1.87(1.38–2.53)	
				≥35	2.47(1.72–3.53)	

Table 1. Study characteristics of published cohort studies on BMI and risk of RCC (Continued)

Author, year, country	Study name or source, study period, duration of follow-up	Study size, sex, age, number of cases	Assessment method of weight/height	BMI (kg/m^2)	RR(95%CI)	Adjustment factors
					W 1.00(Reference)	
					1.11(0.74–1.65)	
					1.57(1.07–2.29)	
					1.60(1.05–2.44)	
					2.16(1.47–3.17)	
					2.59(1.70–3.96)	
Song *et al.*, 2008, Korea	KMIC, 1994.10.1–2003.12.31, 8.75y	154,693, W, 40–64y, 111	Measured	18.5–20.9	0.99(0.29–3.37)	Age, height, smoking status, alcohol intake, physical exercise, and pay level at study entry, after excluding the cancer patients diagnosed within the first 5 years of follow-up
				21.0–22.9	1.00(reference)	
				23.0–24.9	1.64(0.66–4.06)	
				25.0–26.9	2.16(0.88–5.30)	
				27.0–29.9	2.12(0.81–5.58)	
				≥30	3.25(0.95–11.1)	
Setiawan *et al.*, 2007, USA	HLAMC, 1993–2002, 8.3y	161,126(M 75,162, W 85,964), M/W, 65(45–75) y, 347(M 220, W 127)	Self-reported	<25	M 1.00(Reference)	BMI, smoking, alcohol drinking, hypertension, and physical activity as appropriate
				25–30	1.14(0.84–1.55)	
				≥30	1.76(1.20–2.58)	
					W 1.00(Reference)	
					2.03(1.31–3.15)	
					2.27(1.37–3.74)	
Reeves *et al.*, 2007, UK	MWC, 1996–2001, 5.4y	122,2630, W, 55.9(50–64)y, 723	Self-reported	<22.5	0.95(0.79–1.14)	Age, geographical region, socioeconomic status, reproductive history, smoking status, alcohol intake, physical activity, and, where appropriate, time since menopause and use of hormone replacement therapy
				22.5–24.9	1.00(Reference)	
				25–27.4	1.10(0.94–1.28)	
				27.5–29.5	1.19(0.99–1.44)	
				≥30	1.52(1.31–1.77)	

Table 1. Study characteristics of published cohort studies on BMI and risk of RCC (Continued)

Author, year, country	Study name or source, study period, duration of follow-up	Study size, sex, age, number of cases	Assessment method of weight/height	BMI (kg/m^2)	RR(95%CI)	Adjustment factors
Luo *et al.*, 2007, USA	WHI, 1993.9–2005.9.12, 7.7y	140,057, W, 50–79y, 269	Measured	<25.0	1.0(Reference)	Participation in the observational study or clinical trials, and different treatment assignments for all three clinical trials, age, smoking status, hypertension, oral contraceptive use, and total energy intake
				25–29.9	1.2(0.9–1.7)	
				30.0–34.9	1.5(1.0–2.1)	
				≥35.0	1.6(1.1–2.4)	
Lukanova *et al.*, 2006, Sweden	NSHDC, 1985–2003, (M 8.2 ± 3.6y; W 8.3 ± 3.5y)	68,786(M 33,424; W 35,362), M/W, (M 46 ± 9.8y; W 46.1 ± 9.7y), 45(M 25; W 20)	Measured	18.5–24.9	M 1.00(Reference)	Age, calendar year and smoking, all subjects
				25–29.9	1.30(0.51–3.56)	
				≥30	3.63(1.23–10.66)	
					W 1.00(Reference)	
					0.92(0.31–2.58)	
					1.79(0.55–5.27)	
Pischon *et al.*, 2006, Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden and UK	EPIC, 1992–2000, 6.0 ± 1.6y	348,550, M/W, 51.6(25–70)y, 287(M 155, W 132)	Measured	M <23.6	M 1.00(Reference)	Smoking status, education, alcohol consumption and physical activity, using age as the underlying time variable, and stratified by center and age at recruitment
				23.6–25.3	1.07(0.65–1.77)	
				25.4–27	0.67(0.39–1.18)	
				27.1–29.3	0.84(0.49–1.43)	
				≥29.4	1.22(0.74–2.03)	
				W <21.8	W 1.00(Reference)	
				21.8–23.7	1.48(0.73–3.01)	
				23.8–25.9	1.39(0.69–2.80)	
				26–29	1.99(1.03–3.88)	
				≥29.1	2.25(1.14–4.44)	

Table 1. Study characteristics of published cohort studies on BMI and risk of RCC (Continued)

Author, year, country	Study name or source, study period, duration of follow-up	Study size, sex, age, number of cases	Assessment method of weight/height	BMI (kg/m^2)	RR(95%CI)	Adjustment factors
Samanic *et al*., 2006, Sweden	SFOSHCI, 1971–1992, 19y	362,552, M, 34.3y, 820	Measured	18.5–24.9	1.00(Reference)	Attained age (10-year intervals) and calendar year (5-year intervals), and smoking status (never, former, current, unknown), and relative to normal weight subjects, diastolic blood pressure (continuous)
				25–29.9	1.28(1.10–1.49)	
				≥30	1.82(1.41–2.35)	
Oh *et al*., 2005, Korea	KNHIC, 1992–2001.12.31, 10y	781,283, M, ≥20 y, 443	Measured	18.5–22.9	1.00(Reference)	Age, smoking status, average amount of alcohol consumed per day, frequency of regular exercise ore than 30 minutes during a week, family history of cancer, and residency area at baseline
				23.0–24.9	1.06(0.84–1.34)	
				25.0–26.9	1.23(0.94–1.61)	
				27.0–29.9	1.89(1.37–2.60)	
				≥30.0	1.62(0.66–3.94)	
Flaherty *et al*., 2005, USA	NHS and HPFS, 1976–2000.5.31, (M 12y; W 24y)	167,144(M 48,953; W 118,191), M/W, 30–75 y, 265(M 110; W 155)	Self-reported	M <22.0	M 1.0(Reference)	Age, hypertension and pack–years of smoking
				22.0–24.9	2.1(0.7–5.9)	
				25.0–27.9	2.4(0.9–6.8)	
				28.0–29.9	2.1(0.7–6.6)	
				≥30.0	2.1(0.7–6.8)	
				W <22.0	W 1.0(Reference)	
				22.0–24.9	1.3(0.9–2.0)	
				25.0–27.9	1.6(0.9–2.5)	
				28.0–29.9	2.2(1.2–4.1)	
van Dijk *et al*., 2004, Netherlands	NCSDC, 1986.9–1995.12, 9.3 y	120,852, M/W, 55–69y, 264	Self-reported	<23	0.77(0.50–1.19)	Age, sex, smoking, energy intake, non-occupational physical activity, and, en only, occupational physical activity
				23–25	1.00(Reference)	
				25–27	0.92(0.61–1.38)	
				27–30	1.46(0.97–2.21)	
				≥30	1.04(0.54–1.99)	

Table 1. Study characteristics of published cohort studies on BMI and risk of RCC (Continued)

Author, year, country	Study name or source, study period, duration of follow-up	Study size, sex, age, number of cases	Assessment method of weight/height	BMI (kg/m^2)	RR(95%CI)	Adjustment factors
Nicodemus *et al.*, 2004, USA	IWHS, 1986–2000, >15	34,637, W, 55–69y, 124	Self-reported	<22.9	1.0(Reference)	Age
				22.9–25.0	0.80(0.38–1.65)	
				25.0–27.4	1.46(0.77–2.74)	
				27.4–30.6	1.87(1.02–3.41)	
				>30.6	2.49(1.39–4.44)	
Bjorge *et al.*, 2004, Norway	DRSN and CRN, 1963–2001, 23(0–40) y	2,001,230(M 963,442; W 1,037,788), M/W, 20–74y, 6453(M 3821; W 2632)	Measured	18.5–24.9	M 1.00(Reference)	Age at height and weight measurement and birth cohort
				25.0–29.9	1.18(1.11–1.26)	
				≥30.0	1.55(1.36–1.76)	
					W 1.00(Reference)	
					1.32(1.21–1.45)	
					1.85(1.66–2.06)	
Calle *et al.*, 2003, USA	CPS II, 1982–1998, 16y	900,053(M 404,576; W 495,477), M/W, 57y, 1310(M 837; W 473)	Self-reported	M 18.5–24.9	M 1.00(Reference)	Age, education, smoking status and number of cigarettes smoked, physical activity, alcohol use, marital status, ethnic group, aspirin use, fat consumption, and vegetable consumption.
				25.0–29.9	1.18(1.02–1.37)	
				30.0–34.9	1.36(1.06–1.74)	
				≥35	1.70(0.99–2.92)	
				W 18.5–24.9	W 1.00(Reference)	
				25.0–29.9	1.33(1.08–1.63)	
				30.0–34.9	1.66(1.23–2.24)	
				35.0–39.9	1.70(0.94–3.05)	
				≥40.0	4.75(2.50–9.04)	

BMI, body mass index; RCC, renal cell cancer; RR, relative risk; CI, confidence interval; Me-Can, Metabolic syndrome and Cancer project; NA, not available; M, men; W, women; CNBSS, Canadian National Breast Screening Study; NIH-AARP, National Institutes of Health-AARP Diet and Health Study; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; INCR, Israel National Cancer Registry; VITAL, Vitamins and Lifestyle Study; AMORIS, Apolipoprotein Mortality Risk; JPHCPS, Japan Public Health Center-based Prospective Study; NLCS, Netherlands Cohort Study; KMIC, Korea Medical Insurance Corporation; HLAMC, Hawaii-Los Angeles Multiethnic Cohort; MWC, Million Women Study; WHI, Women's Health Initiative; NSHDC, Northern Sweden Health and Disease Cohort; EPIC, European Prospective Investigation into Cancer and Nutrition; SFOSHCI, Swedish Foundation for Occupational Safety and Health of the Construction Industry; KNHIC, Korea National Health Insurance Corporation; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; NCSDC, Netherlands Cohort Study on Diet and Cancer; IWHS, Iowa Women's Health Study; DRSN, Death Registry at Statistics Norway; CRN, Cancer Registry of Norway; CPS II, Cancer Prevention Study II.

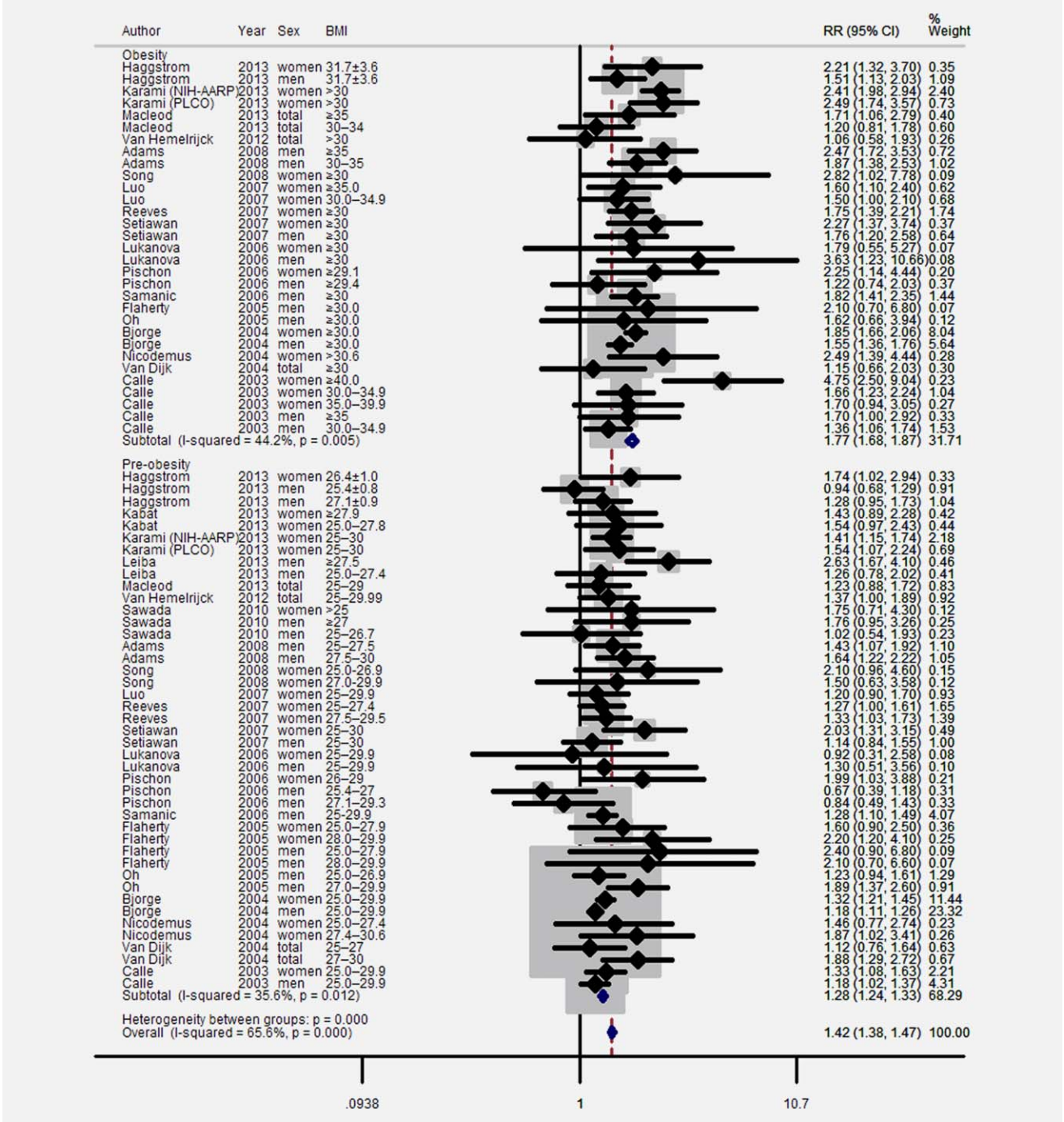

Figure 2. Forest plot of RRs of overweight (*i.e.*, preobesity and obesity) *vs*. normal weight for BMI with RCC risk. Open diamond denote the pooled RR. Black squares indicate the RR in each study, with the square sizes inversely proportional to the standard error of the RR. Horizontal lines represent the 95%CIs. RR, relative risk; CI, confidence interval; BMI, body mass index; RCC, renal cell cancer. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

pooled RRs ranged from 1.38 to 1.47 for preobesity and from 1.68 to 1.87 for obesity, respectively, which indicated that the pooled estimates were robust and not influenced by a single study. The sensitivity analysis performed with four knots at percentiles 5, 35, 65 and 95% of the distribution obtained similar results with the former dose–response meta-analysis.

Publication bias. The Egger's test showed the possibility of publication bias for the analysis ($p = 0.001$) although the Begg's test was not statistically significant ($z = 1.40$, $p = 0.160$). Because of this, we undertook the "trim and fill" analysis, which conservatively imputes hypothetical negative unpublished studies to mirror the positive studies that cause publication bias. The pooled RR(95%CI) incorporating the

Table 2. Subgroup analyses of BMI and RCC

	Preobesity			Obesity		
Study	No. of studies	RR(95%CI)	I^2 (%)	No. of studies	RR (95%CI)	I^2 (%)
All studies	21	1.28(1.24–1.33)	35.6	18	1.77(1.68–1.87)	44.2
Sex						
Men	12	1.22(1.17–1.28)	53.2	10	1.63(1.50–1.77)	17.2
Women	14	1.38(1.29–1.47)	0.0	11	1.95(1.81–2.10)	34.9
Combined	3	1.37(1.15–1.63)	28.9	3	1.28(1.00–1.63)	0.0
Study location						
North America	9	1.36(1.26–1.47)	1.0	8	1.89(1.73–2.07)	54.1
Europe	8	1.23(1.18–1.29)	36.5	8	1.70(1.59–1.82)	25.4
Asia	4	1.56(1.34–1.82)	37.6	2	2.06(1.05–4.03)	0.0
Assessment of weight/height						
Measured	10	1.25(1.20–1.31)	50.2	8	1.71(1.59–1.83)	13.3
Self–reported	11	1.34(1.26–1.43)	14.8	10	1.86(1.72–2.02)	53.4
Duration of follow-up						
≥10 years	13	1.28(1.23–1.33)	40.7	10	1.78(1.67–1.89)	59.5
<10 years	8	1.32(1.19–1.45)	27.7	8	1.76(1.57–1.97)	8.7
Adjustment factors						
Age						
Yes	17	1.27(1.22–1.32)	27.4	15	1.71(1.62–1.82)	30.7
No	4	1.47(1.30–1.65)	49.9	3	2.19(1.90–2.54)	51.6
Smoking						
Yes	17	1.33(1.26–1.40)	22.2	15	1.82(1.69–1.96)	41.4
No	4	1.25(1.18–1.31)	65.4	3	1.72(1.58–1.86)	63.9
Physical activity						
Yes	9	1.33(1.24–1.42)	40.0	8	1.75(1.58–1.94)	40.8
No	12	1.27(1.21–1.32)	31.9	10	1.78(1.67–1.90)	50.2
Alcohol consumption						
Yes	8	1.29(1.19–1.39)	35.9	7	1.66(1.49–1.85)	36.4
No	13	1.28(1.23–1.34)	37.8	11	1.81(1.70–1.93)	49.2
Hypertension						
Yes	7	1.36(1.25–1.49)	0.0	6	1.93(1.74–2.16)	44.2
No	14	1.27(1.22–1.32)	44.2	12	1.72(1.62–1.83)	41.9

BMI, body mass index; RCC, renal cell cancer; RR, relative risk; CI, confidence interval.

hypothetical studies was 1.38(1.29–1.48), which did not virtually change the results.

Discussion

In our meta-analysis, the significant association between overweight (*i.e.,* obesity and preobesity) and increased risk of RCC was observed both in men and women, and the risk was slightly higher in women than in men. The dose–response analysis showed that each 1 kg/m^2 increment of BMI corresponded to a 4% increase in risk of RCC. However, it was just an estimate that broke down in the higher BMI categories. A statistically nonlinear relationship between BMI and RCC risk was also found, even though adjusted for other known risk factors.

A previous quantitative review by Bergström *et al.*[7] examined the relationship between BMI and risk of RCC. Similarly, it reported a summary RR(95%CI) of 1.07(1.05–1.09) per unit increase of BMI. Although it included 22 studies, most of these were case–control studies and only a few were cohort studies. Furthermore, it showed that increased BMI was equally strongly associated with an increased risk of RCC among men and women, which was not completely consistent with the results of our study and a recent meta-analysis. Ildaphonse et al.[8] and Mathew et al.[9] reported a slightly lower association between BMI and increased renal cancer, and the pooled risk was slightly greater in women (RR = 1.06, 95%CI = 1.05–1.07) than in men (RR = 1.05,

95%CI = 1.04–1.06). However, they did not examine the possibility of the nonlinear associations between them. Our results, only based on cohort studies, were generally in line with the results from the previous meta-analysis.[8,9] Moreover, we also found a statistically nonlinear dose-response relationship between BMI and risk of RCC, both for men and women. Subgroup analysis by the potential confounding factors showed basically stable results as well.

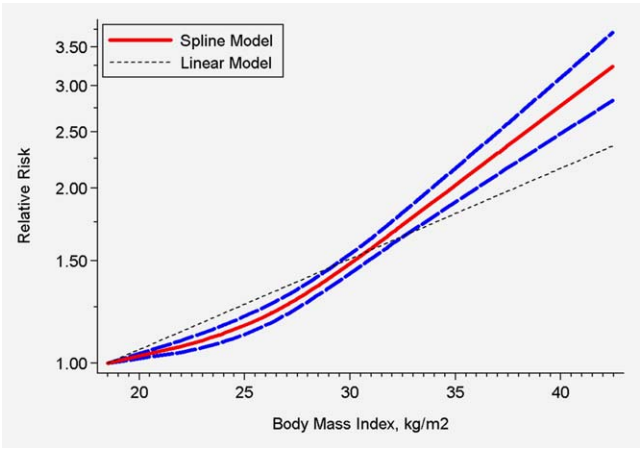

Figure 3. The dose–response analysis between BMI and RCC risk in cohort studies with restricted cubic splines in a multivariate random-effects dose–response model. The solid line and the long dash line represent the estimated RR and its 95% CI. Short dash line represents the linear relationship (per 1 kg/m^2 increment). BMI, body mass index; RCC, renal cell cancer. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Obesity might be associated with increased risk of kidney cancer through several hormonal mechanisms. Increasing BMI is associated with elevated levels of free insulin growth factor-1,[42] which contributes to the stimulation of renal cell proliferation and inhibition of apoptosis.[43] Obesity also affects the hormonal milieu by increasing levels of free endogenous oestrogen,[44] which may in turn influence renal cell proliferation and growth by direct endocrine receptor-mediated effects, by regulation of receptor concentrations or through paracrine growth factors. In addition, obese individuals have been reported to have higher glomerular filtration rate and renal plasma flow, which may increase the risk of kidney damage,[45,46] and thereby render the kidney more susceptible to carcinogens.

Besides obesity, other known risk factors such as sex, age, smoking, and hypertension are also related to RCC.[1] A large number of included studies did not report all of the risk factors, although we extracted the RRs that reflected the greatest degree of control for potential confounders. However, these factors just affected magnitude of the association between BMI and RCC. Subgroup analysis showed that studies controlling for age and men revealed a slightly lower summary RR than other studies, while those controlling for women, smoking, and hypertension revealed a slightly higher RR than others. In addition, dose–response meta-analyses by adjustment of these factors also indicated a significant nonlinear relationship between BMI and increased risk of RCC, and there was no change to direction of the results.

Strengths of our study were the inclusion of cohort studies only, the large number of subjects and cases, and the assessment of potential nonlinear relationships. Dose–response

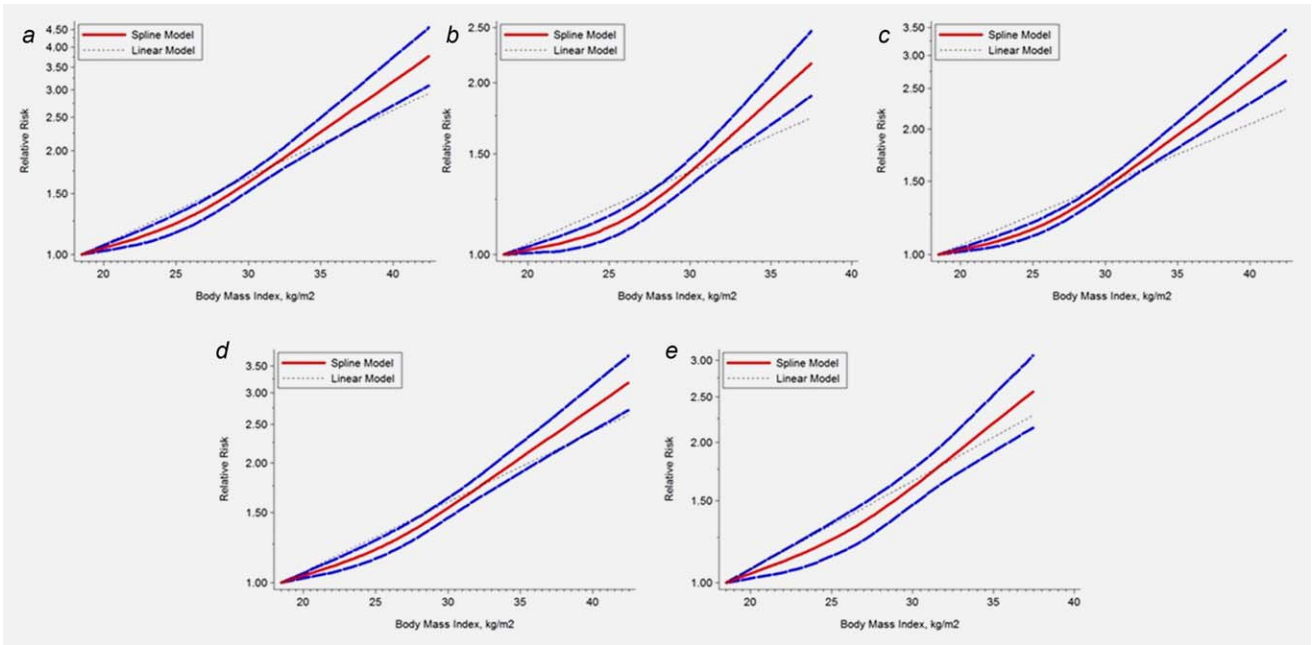

Figure 4. The dose–response analysis between BMI and RCC risk by adjustment of: (*a*) women; (*b*) men; (*c*) age; (*d*) smoking and (*e*) hypertension. The solid line and the long dash line represent the estimated RR and its 95% CI. Short dash line represents the linear relationship (per 1 kg/m^2 increment). BMI, body mass index; RCC, renal cell cancer. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

analysis was also performed to better describe the association of RCC risk with BMI. Except for that described above, there were also some other limitations in this meta-analysis. First, in our meta-analysis including only published studies, it is inevitable that an observed effect might suffer from publication bias because studies with null results tend not to be published. Interestingly, the "trim and fill" analysis showed that publication bias did not appreciably affect our results. Second, studies had examined risk by quartile distribution (cut-off point) of BMI, and cut-offs often varied across studies. Therefore, some of studies which showed the RRs in preobesity (*e.g.,* BMI > 27 kg/m^2) also included the obesity people according to the predefined criteria. The deficiency of criteria might influence the accuracy of our results to some extent.

In conclusion, our meta-analysis confirms that increased BMI are associated with increased risk of RCC. A statistically nonlinear relationship between BMI and RCC risk is also found. The association is observed both in men and women.

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Appendix

PubMed

((Obesity OR Obese OR Adiposity OR fat OR fatness OR BMI OR "Body Mass Index" OR "body size" OR Overweight OR weight)) AND ((renal OR kidney) AND (cancer OR cancers OR carcinoma)) AND "cohort studies"[mh]

Embase

((Obesity OR Obese OR Adiposity OR fat OR fatness OR BMI OR "Body Mass Index" OR "body size" OR Overweight OR weight)) AND ((renal OR kidney) AND (cancer OR cancers OR carcinoma)) AND 'cohort studies'/exp